[2.0] 7.0 micrometers. /B

A2 cont. B

7. (Amended) The process of claim 1, wherein the average particle size distribution is from about 1.0 to about [7] 2.0 micrometers.

REMARKS

The OFFICIAL ACTION and the cited references have been carefully reviewed.

The review indicates that the claims, especially as amended, recite patentable subject matter and should be allowed. Reconsideration and allowance therefore respectfully requested.

Before contending with the grounds upon which the rejection is based, it is useful to briefly summarize the essentials of the process for preparing Biodegradable Microspheres of predetermined average particle size distributions of the invention by controlling the viscosity of the emulsion in which the microspheres of biodegradable polymers are formed.

Applicants are the first to invent a modified solvent extraction process for preparing microspheres of a poly (DL-lactide-co-glycolide) biodegradable polymer having a predetermined average particle size distribution such that, there is maximal uptake of the microspheres by both M Cells and non-M Cells, either in the villous epithelium or in the Peyer's patches

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follicle associated epithelium, when using the polymer as a carrier of immunogens for immunization in mammals.

This has unexpectedly been accomplished by modifying the solvent extraction process for producing microspheres so that the average particle size distribution is controlled by altering the viscosity of the emulsion, either by:

1) Predilution of the emulsion oil with acetonitrile solvent;

2) Adding thickening agents such as polybutylene to the emulsion oil to deliberately increase it's viscosity;

3) Employing the use of oils with predefined viscosities for preparation of the emulsion; or

4) By deliberately adjusting the viscosity of paraffin oil used in the emulsification process by preheating paraffin oil to a temperature which yields the desired viscosity.

In the context of the invention, it has found that, the oil viscosity is the primary process parameter in determining the average distribution of particle size ranges of the microspheres diameter.

Claims 1-11 are present in the application. Claims 10 & 11 have been withdrawn from consideration, and claims 1-9 were elected for examination purposes. Therefore, the claims for consideratiion are now claims 1-9.

Claims 1-9 were rejected as being unpatentable over Tice et al. '84, under 35 U.S.C. § 103.

Applicants respectfully traverse the rejection and request reconsideration for the reasons hereinafter set forth.

Tice et al. discloses an anti-inflammatory agent containing microparticle compositions prepared by dissolving an anti-inflammatory agent in a solvent selected from the group consisting of acetone, a halogenated hydrocarbon, an aromatic hydrocarbon, a halogenated aromatic hydrocarbon, a cyclic ether, an alcohol and water and dissolving a biocompatible and biodegradable wall forming material in the solvent; dispersing the solvent containing the anti-inflammatory agent and wall forming material in a continuous phase processing medium of water, toluene, xylene, a synthetic oil or a natural oil; evaporating a portion of the solvent from the dispersion step to form microparticles containing the anti-inflammatory agent in suspension; and extracting the remainder of the solvent from the microparticles.

On the other hand, and by contrast, the process of the process invention utilizes the different solvent of acetonitrile, which does not belong to any of the classes of solvents disclosed and claimed in the Tice et al. patent (see Tice et al patent at column 3, lines 24-31).

Further, it should be noted that the process of the present invention first lyophilizes an antigen-sucrose to make a

hydrophilic matrix prior to dispersal of the matrix into the acetonitrile solvent. This lyophilizing step stabilizes and isolates the antigen being encapsulated from the solvents in the process.

Tice et al., on the other hand, requires direct dispersal or dissolving of the active agent into the same non-acetonitrile solvents used to dissolve the polymer.

In connection with Tice et al., it is necessary for Tice et al. "to prevent microparticles from agglomerating and to control the size of the solvent microdroplets in the emulsion", by the use of a surfactant (see column 3, lines 32-55).

By virtue of the lyophilized step and the use of a controlled viscosity emulsion, applicants do not have to use surfactants as a means of controlling particle size or as a means of preventing agglomeration of the polymer particles.

Instead, the present invention utilizes the emulsion viscosity exclusively as a means of controlling sphere size, and emphasizes maintaining uniformity of the emulsions viscosity as the means of preventing agglomeration of particles during the emulsification process.

Tice et al. discloses that temperature during the formation of the emulsion is not especially critical but can influence size and quality of microparticles and the solubility of the drug in the continuous phase (column 3, lines 51-70 and column 4 , lines 1-2).

The process of the present invention is directly opposite to Tice et al.'s disclosure that the temperature of the emulsion is critical to influence the size and quality of the microparticles and the solubility of the drug in the continuous phase.

In the process of the present invention, increasing the emulsion temperature results in a reduction of the emulsion viscosity, which in turn results in a predictable increase in sphere diameter over a wide range of mixing parameters. Further, in the process of the present invention, the viscosity of the emulsion oil is the principle and predictable determinant of the diameters of the final microsphere population produced (for example, the temperature of the external phase (heptane) has only a minor influence on the final product, since the core material is coated with a hydrophilic substance i.e. sucrose, it is partially protected from dissolution into the hydrophobic organic extractant.

Further still, the Tice et al. disclosure specifically states that the "solvent can easily be removed [from the emulsion] by common techniques such as heating, the application of a reduced pressure or a combination of both." (see column 4, lines 5-17).

By contrast, the present invention process does not rely on the use of heating or reduced pressure to evaporate the solvent from the emulsion. Instead, the invention relies on the

use of a second organic solvent in which all of the emulsion components other than the polymer and the core are soluble. The unwanted emulsion components are extracted by this solvent rather than evaporated.

The sole process disclosed by Tice et al. is that of a solvent evaporation technique which uses water as it's external phase and evaporation as a means of removing the solvent into which the polymer was solubilized. On the other hand, it has been made abundantly clear in the foregoing discussion that the process of the present invention uses a hydrophobic external phase and a second organic solvent to extract the first solvent.

Finally, in order to function as a vaccine antigen depot, microspheres must retain the majority of their core for at least several weeks. If the vaccine micro capsules are intended to function as vehicles for delivery of antigen into antigen presenting cells such as microphages, the microcapsules must:

1) Be less than 10 microns in diameter so that they can be readily phagocytized; and

2) Retain the majority of their core for at least 2 days to assure that the core has not leaked out prior to uptake of the microsphere by an APC. The process of the present invention predictably yields microspheres in which diameters are within the 1-10 micron range, and the present process protects the conformation of antigen by flash freezing (lyophilizing) the antigen into sucrose. After the initial freezing, the antigen is

not rehydrated until its release from the sphere. The formulation described by Tice et al. has a 1-2 hour release curve ± 100% of the core is released within 2 hours, thereby rendering it of little value as vaccine adjuvant, and also of little value for efficacious sustained drug release. Most drug half-lives are such that the efficacious systemic levels remain for 2-8 hours past dosing.

Accordingly, in view of the foregoing discussions, detailing the glaring differences between the disclosure of Tice et al. versus the requirements of the process of the present invention, it is manifestly clear that Tice et al. fails to render the process of the present invention obvious in accordance with requirements of 35 U.S.C. § 103.

Withdrawal of the rejection is respectfully requested.

Claims 1-9 were rejected under 35 U.S.C. § 112, first paragraph, on the allegation that the disclosure is enabling for claims limited to solvents and polymer to be used in the claimed process; however, in view of the amendments made to the claims, it is believed that the rejection is no longer applicable.

Note is taken of the cited but non-applied reference of Fong; however, contrary to the assertions made in the OFFICIAL ACTION, applicant's process is not disclosed or known in the prior art at all; let alone to prevent microspheres from agglomerating, inasmuch as the prior art fails to hint, suggest or teach applicants' process.

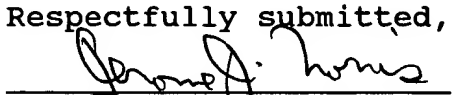
The OFFICIAL ACTION made reference to the inadvertent omissions of Tables 3 and 4.

These tables are enclosed herewith.

Note is taken of indication that the drawings are informal; however, it is respectfully requested that the holding of informality be kept in abeyance until such time as there is notification of allowable subject matter, after which applicants will provide formal drawings.

In view of the foregoing amendments, remarks and arguments, it is believed that the application is now in condition for allowance, and early notification of the same is earnestly solicited.

Respectfully submitted,



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